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Case review

The changing face of the 'royal disease' – Medicolegal aspects of haemophilia

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ABSTRACT

Haemophilia represents a group of heritable disorders caused by deficiencies in plasma proteins that are involved in coagulation. The case of a two-year-old boy with an established diagnosis of haemophilia B is reported to demonstrate a rare cause of unexpected death. He had a recent history of epistaxis and was found unexpectedly dead. At autopsy the posterior pharynx was obstructed by blood clot with aspirated blood within the distal airways of the lungs, and melena throughout both small and large intestines. His death was due to haemorrhage and airway obstruction complicating epistaxis. The profile of individuals with haemophilia has been changing in recent years with less deaths from haemorrhage due to improved clinical management. As the life expectancy of these patients is increasing, forensic examiners will now have to consider not only possible haemorrhagic causes of death but will also have to determine the significance of more long standing infectious processes related to human immunodeficiency virus (HIV) and hepatitis C from contaminated transfusions, in addition to evaluating the role of the more usual diseases related to age.

1. Introduction

Haemophilia represents a group of heritable disorders manifested by deficiencies in plasma proteins that are integral to the maintenance of the normal processes of coagulation. The two most common are haemophilia A and B.[1] Also known as the 'royal disease', haemophilia was responsible for the deaths of a number of descendents of Queen Victoria and played a considerable role in the fate of the Romanov dynasty in Russia after it was discovered that the Tsarevich Alexis was suffering from haemophilia B.[2]

While most individuals with haemophilia have an established diagnosis, cases may come to forensic attention for the assessment of sudden and/or unexpected death, complications of therapy, and problems that may occur in distinguishing accidental from inflicted injury, particularly in the young. The literature is reviewed and a case of a child with established haemophilia B is reported to demonstrate an unusual cause of sudden death. The definition of sudden death is quite variable, with different authors setting limits of zero, one, six and 24 h from the time of onset of symptoms and signs to the time of death. Cases have been included in this paper if decedents were either completely well, or had been suffering from only an apparently minor illness immediately before death. If a major illness was present it was thought to be stable. The term "unexpected" is used if a death occurred before it was anticipated.[3]

2. Case report

A two-year-old boy with an established diagnosis of haemophilia B (Factor IX level 2%) was found dead face down on his bed. He had a recent history of epistaxis three days before death, unrelated to trauma, which necessitated hospitalization and an infusion of factor IX. No further bleeding had occurred and his haemoglobin had stabilized at 85 gm/L.

At autopsy scattered bruises of variable ages were present on the face, head chest and limbs which were considered to be a manifestation of his underlying bleeding disorder. A 2 cm diameter blood clot was found obstructing the posterior nasopharynx with aspirated blood within the distal airways of the lower lobes of the lungs bilaterally. While no fresh blood was found within the stomach, melena was present throughout both small and large intestines. A skeletal survey revealed no fractures and formal neuropathological assessment of the brain was normal. There was no evidence of other trauma and no other underlying conditions were present that could have caused or contributed to death. Death

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was therefore attributed to haemorrhage and airway obstruction complicating epistaxis in a child with haemophilia B.

3. Discussion

Spontaneous haemorrhage, or significant haemorrhage following relatively low-force trauma, may occur from a variety of congenital or acquired conditions. Vascular disorders may involve anatomically abnormal arteriovenous malformations,[4,5] or intrinsic defects in the structure of vessel walls due to connective tissue disorders such as Marfan or Ehlers-Danlos syndromes.[6,7] Abnormalities of circulating blood components may also result in haemorrhage being the first manifestation of haematopoietic malignancies such as leukaemia, or conditions such as idiopathic thrombocytopenia purpura.[3]

Disturbances of components of the blood coagulation pathways are less common, but are additional well-recognized causes of sometimes massive and fatal haemorrhage. The most common inherited disorders of coagulation involve factor VIII (haemophilia A), factor IX (haemophilia B or Christmas disease), and von Willebrand factor (the latter with an incidence of around 1% of the population).[1] Haemophilia C due to a deficiency in Factor XI is found less often.[1] In addition, there are also numbers of other less common deficiencies.[8] Haemophilia A is an X-linked recessive disorder with an incidence of approximately 1 per 5000–10,000 male births that is caused by deficiency in the plasma clotting factor VIII.[9] Haemophilia B due to deficiency of factor IX is also an X-linked recessive disorder that accounts for approximately 20% of haemophilia cases.[10] The gene for haemophilia A is located at Xq28, and for haemophilia B at Xq27.[1]

The heritable nature of bleeding disorders has been recognized for many centuries, with the Talmud forbidding further circumcision in a family if two successive boys had bled to death from the procedure.[11] In the nineteenth century Grandidier, a French medical practitioner, advised that "all members of bleeder families should be advised against marriage" and those with haemophilia were sensibly instructed not to take up duelling.[11] However, it is now recognized that at least 25% of cases of newly diagnosed haemophilia represent spontaneous mutations.[10]

The life expectancy of haemophiliacs has increased dramatically in recent decades due to improvements in treatment resulting in a relatively normal life expectancy, compared to death in childhood or adolescence previously.[1] A study in the United Kingdom of patients without HIV infection showed a median life expectancy in severe haemophilia of 63 years, and of 75 years in mild to moderate haemophilia.[12] A result of this will be the increasing incidence of usual age-related illnesses such as malignancy and cardiovascular disease in this group that will present as co-morbidities.[13,14]

At the beginning of life, delivery usually occurs without problems, although there is a 1–4% incidence of intracranial haemorrhage within the first month.[1] Symptoms do not generally occur until an infant begins to crawl or walk, with the first manifestation in severe cases usually being haemorrhage into a joint space before the age of four years.[1]

Sudden and/or unexpected death may occur, most often resulting from intracranial haemorrhage. There was an estimated incidence of 2.5 episodes of intracranial haemorrhage per 100 patients per year in an Italian cohort, most of which were associated with survival. Those under two years of age were at greatest risk, with a further increase in risk after 40 years of age. Intraparenchymal haemorrhage occurred in 43.7% of cases and subdural haemorrhage in 26.8%.[15] Three and a half to four percent of male neonates with haemophilia will suffer intracranial haemorrhage, a rate which is 40–80 times normal,[16] and on occasion this may be the first manifestation of their clotting disorder.[10] The risk of central nervous system haemorrhage is greatest in those with the most severe factor deficiencies (<1% of normal circulating factor) and in those with inhibitors.[7,17]

Haemorrhages are more often spontaneous than associated with trauma,[18] a situation exemplified by a 14-year-old boy with haemophilia A who had been observed in hospital for three days following a fall with concussion. He appeared quite well at the end of this time and so was discharged home, only to be admitted several days later with an acute massive intracerebral haemorrhage and death within 24 h. There was no history of additional head trauma.[3]

Haemophilia may also worsen underlying injuries that may not necessarily have been lethal in an individual with normal clotting parameters. A good example from history is Queen Victoria's son Leopold, the first "bleeder prince", who died of a cerebral haemorrhage following a fall with only a minor blow to the head.[11,19] Another example involves damage to the posterior pharyngeal wall in a child who has fallen with an object such as a pencil in the mouth. Haemophilia may predispose to massive and rapid retropharyngeal haemorrhage with life-threatening upper airway obstruction.

The nature of mortality associated with haemophilia has changed over recent years with improved therapy. While haemorrhage was once the major cause of death, a recent Italian national study has shown human immunodeficiency virus (HIV) infection to be the major cause of death (in 45% of cases) with 13% of deaths associated with complications of hepatitis-C.[20] Thus, at autopsy in addition to looking for signs of haemorrhage it is also important to check for evidence of these transfusion transmitted infections that were spread through contaminated blood-product infusions prior to the introduction of viral inactivation techniques in 1986.[1] It was estimated that 1200 haemophiliacs were infected in the United Kingdom alone between 1979 and 1985.[1] This means that medicolegal facilities dealing with these cases must use special precautions at autopsy. The infections may also have played a role in the terminal episode with, for example, sepsis, cardiac disease, central nervous system involvement and autonomic neuropathy associated with HIV infections causing arrhythmias, haemodynamic instability and cardiorespiratory arrest.[21] Less common findings at autopsy include gastrointestinal bleeding from ulcers or gastritis,[22] sometimes with acute or subacute intestinal obstruction from intramural haematomas.[23] Hepatitis C related cirrhosis may exacerbate bleeding tendencies.

Airway compromise may occur in haemophilia if haemorrhage into soft tissues of the neck causes swelling with compression of upper airways. This may not be an immediate effect as slow seepage of blood may take some time to reach a critical level. A similar phenomenon has been observed following cervical spinal fusion without injury to major vessels in those with normal coagulation.[24] A case of acute airway obstruction 16 h after manual strangulation in a haemophiliac has been reported where critical luminal narrowing was associated with submucosal haemorrhage.[25]

In infants and young children the finding of multiple bruises should always raise the possibility of inflicted injury, however, in those with haemophilia the bruising may be out of proportion to the degree of injury and may represent an exaggerated tissue response to accidental trauma.[3] The absence of bone fractures and internal organ lacerations or haematomas, as in the reported case, would also be in keeping with accidental injury. Having recognized this possibility, however, it should be remembered that haemophilia is not protective against inflicted injury, and dealing with a seriously and chronically ill child does bring with it significant extra stresses for carers. Determining likely scenarios may, however, be quite complicated as, for example, bilateral retinal haemorrhages have been described in an infant with a space occupying subdural haemorrhage who was subsequently found to

have von Willebrand disease.[26] Other cases of suspected abuse that were found to be related to bleeding disorders included a girl with haemophilia A presenting with a haemarthrosis of the knee, and an infant with head trauma who was diagnosed after prolonged bleeding was noted at surgery.[27]

Acquired haemophilia A should be briefly mentioned. It is a rare condition where autoantibodies develop against factor VIII, usually in later life or during pregnancy. The condition may be idiopathic or associated with a number of different autoimmune and inflammatory disorders. Death may result from haemorrhagic manifestations, such as spontaneous haemothorax, with a mortality rate of 7.9–22%, often in the first few weeks.[28,29]

Of interest, it has been shown that the incidence of myocardial infarction in individuals with severe haemophilia is actually significantly less than in the general age-matched population, presumably because the hypocoagulable state decreases thrombus formation,[13] with relative figures of 0.5 and 4.8% respectively for the two groups in a recent Dutch study.[30] Although surgery was once rarely performed in patients with haemophilia, the advent of cryoprecipitate and clotting factor concentrates has facilitated operative interventions with lower morbidity and mortality rates.[31]

In conclusion, while unexpected death due to haemorrhage remains a potential problem for individuals with haemophilia (as demonstrated by the reported case) there has been a change in the profile of cases with much longer survival and more complications related to HIV and hepatitis C infections. Thus the assessment of cases at autopsy now requires understanding of the possible effects of the underlying haemorrhagic tendency, in addition to transfusion transmitted infections, and usual age-related changes. As well, integrating the scene findings with the pathological and toxicological results is an essential component to the evaluation of these cases.

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Conflicts of interest

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